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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
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07/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,326	HOFFMAN ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28,30,32 and 36-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,30,32 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 26-28, 30, 32, and 36-40 are pending

Applicants' response and amendments to the claims, filed 6/18/2009, are acknowledged and entered. Claims 29, 31, and 33-35 have been cancelled by Applicant. Claims 36-40 are newly added. Claims 26-28, 30, 32, and 36-40 are presented for examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/2009 has been entered.

Response to Arguments

Any previous rejections and/or objections to claims 29, 31, and 33-35 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments have been fully and carefully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Declaration under Rule 1.132

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Arnold Hoffman ("Hoffman" Declaration) and has carefully considered the information provided therein.

Claim Rejections - 35 USC § 112 – Second Paragraph – New Grounds of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-28, 30, 32, and 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Whereas the preamble of amended claim 26 and new claim 36 now recites a method of treating a tumor in a subject, the active method step of the claim recites the step of "...administering to a subject....". This active method step is not linked to the preamble of the claim in such a way so as to clearly convey that "a subject" being administered the claimed compound(s) is the same subject having a tumor comprising malignant cancer cells as recited in the preamble. The Examiner suggests amending claims 26 and 36 to recite "administering to the subject" or "administering to a subject in need thereof".

Claims 26-28, 30, 32, and 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the limitation, "...further comprising a calibrated administration frequency..." so as to continuously maintain a decreased [GSH]2/[GSSH] ratio in malignant cells within a range of from 15 to 75 hours in order to span at least one cell cycle, are not clear. It is not apparent what "administration frequency" is encompassed by the instant claims. For example, an active agent with a long in vivo half-life might only need to be administered once to achieve the claimed result, whereas an active agent with a short in vivo half-life might have to be repeatedly administered to achieve the claimed maintenance of decreased [GSH]2/[GSSH] ratio in malignant cells within a range of from 15 to 75 hours in order to span at least one cell cycle. The instant specification provides no direction with regard to how the administration frequency is calibrated or what administration frequency of the claimed active agents would result in the claimed maintenance of decreased [GSH]2/[GSSH] ratio in malignant cells within a range of from 15 to 75 hours in order to span at least one cell cycle.

Claims 26-28, 30, 32, and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the abbreviations BCNU and BSO. The

first recitation of an abbreviation in the claims should be preceded by the full meaning of the abbreviated term so as to clearly convey what the abbreviation is intended to mean.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-39 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude

extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recite a genus of compounds that is defined only by biological activity (i.e., "E-increasing agent" and "enzyme deactivating agent"). There is insufficient written description of the claimed agents. The specification only discloses GSH-oxidizing agents (page 14, lines 17-25), a genus of compounds that form adducts or conjugate with GSH (page 14, line 26 to page 15, line 23), agents that inhibit GCS or GCL enzymes (page 15, lines 24 to 29), and agents that inhibit/deactivate glutathione reductase (page 16, lines 1-7). The lack of written description of the instantly claimed genus is further compounded by the fact that the agents as instantly claimed must not only have the activity claimed, but must also treat tumors and be capable of maintaining a decreased [GSH]2/[GSSH] ratio in malignant cells. Accordingly, other than those specific compounds disclosed in the specification, Applicants have not demonstrated possession of the claimed "E-increasing agent" and "enzyme deactivating agent" and which further are antitumor agents.

Aside from the very limited group of compounds disclosed in the specification, Applicants provide no direction as to (a) what subset of compounds out of all possible compounds that exist in the art would have been reasonably expected to have activity as "E-increasing agents" or "enzyme deactivating agents" and (b) which of those compounds actually *has* activity in increasing E or deactivating enzymes and further are effective antitumor agents.

Although general techniques such as cellular assays may be known in the art, this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake to even identify, let alone determine the full scope of, the claimed antagonists of "E-increasing agents" or "enzyme deactivating agents", particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

The need for testing amongst varying species of compounds to determine the full scope of the genus of agents instantly claimed demonstrates that Applicants were not in possession of the full scope of the genus now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that

show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of the compounds defined in, e.g., claims 37-39, it remains that the specification provides non-limiting exemplification of a solely functional genus of agents that may be used within the context of the present invention. Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

The same reasoning applies equally to the claimed "wherein said two E-increasing agents *comprise* disulfiram and curcumin" or "wherein said two enzyme deactivating agents *comprise* BCNU and BSO". The word "comprise" as used in the claims suggests that a prodrug or other derivative of the claimed agents is encompassed by the claims, as long as such a prodrug or derivative "comprises" the claimed agent. The fact that one of ordinary skill in the art at the time of the invention would not only need to identify those compounds that are capable of functioning as recited in the claims, but also that they would need to identify, synthesize, and test prodrugs and derivatives of such compounds in numerous disparate types of test cells to determine their activities is clear and unequivocal evidence that Applicants were not in possession of the instantly claimed "E-increasing agents" and "enzyme deactivating agents".

Claim Rejections - 35 USC § 103 – New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims recite methods of treating tumors comprising malignant cancer cells having an operative retinoblastoma protein comprising administering a pharmaceutically effective dosage of a drug comprising a combination of at least one E-increasing agent from the group of disulfiram and curcumin, and at least one enzyme deactivating agent from the group of BCNU and BSO.

Claims 26 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Cen *et al.*** (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204) in view of **Bailey *et al.*** (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796).

Cen *et al.* teach that redox regulation in melanoma cells is aberrant and that disulfiram induces apoptosis of metastatic melanoma cells at a dose of 25-50 ng/mL (Abstract; Fig. 1; Fig. 2). BSO, an inhibitor of γ-glutamyl-cysteine synthetase, as a single agent also increased apoptosis and slightly enhanced the level of apoptosis induced by disulfiram when co-administered for 3 or 4 days (Abstract; Table 1). The authors teach that BSO depletes intracellular glutathione and disulfiram reduces the ratio of reduced and oxidized glutathione (Abstract; Table 2). GSH depletion by BSO was known in the art to enhance the cytotoxic effects of 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, and melphalan, to inhibit DNA

synthesis or growth of melanoma cell lines *in vitro*, and to prolong the survival of melanoma-bearing mice after *in vivo* administration (page 197, right column). BSO alone causes significant apoptosis in tumor cells, especially neuroblastoma (*id.*).

Bailey *et al.* teach that increased intracellular glutathione has long been associated with tumor cell resistance to various cytotoxic agents (Abstract). BSO has been shown to enhance the cytotoxicity of chemotherapeutic agents *in vitro* and *in vivo* (*id.*). The authors studied the effects of BSO combined with melphalan in patients with advanced cancers. BSO was administered by continuous infusion on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours (Abstract). The treatment method produced "consistent, profound glutathione [GSH] depletion" (*id.*; Figure 1; Figure 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered disulfiram and BSO to a subject having cancer, especially melanoma. The skilled artisan would have been motivated to do so because each of these agents alone has been demonstrated to induce apoptosis of melanoma cells and in combination, increased apoptosis over either agent alone is observed. Disulfiram and BSO are taught in the prior art to deplete intracellular glutathione (BSO) and reduce the $[GSH]^2/[GSSG]$ ratio (disulfiram) as recited in the instant claims.

In the absence of evidence to the contrary, the melanoma cells treated in Cen *et al.*, and in fact melanoma cells in a subject, have an "operative retinoblastoma protein" as recited in the instant claims. For example, Applicants teach that human RB protein is expressed in "every tissue type examined" (page 2, lines 28-29), plays a major role in a regulatory circuit in late G_1 (growth) phase (*id.* at lines 29-30), and is involved in regulating an elusive switch point between cell cycle, differentiation, and apoptosis (page 3, lines 3-4). As such, all cells in a subject would be expected to have an operative retinoblastoma protein. The effect recited in the instant claims (*i.e.*, dephosphorylizing the RB protein and maintaining a dephosphorylated state of the RB to induce apoptosis) would be a natural result of contacting melanoma cells in a subject with disulfiram and BSO as suggested and motivated by the prior art. Applicant's recognition of the mechanism through which disulfiram and BSO induce apoptosis of melanoma cells is not a patentable distinction over the treatment method taught in the cited prior art.

Regarding a calibrated administration frequency to continuously maintain decreased [GSH]2/[GSSG] ratio in malignant cells, Cen *et al.* teach such a "calibrated administration frequency" wherein they disclose co-administration for 3 or 4 days. Cen *et al.* additionally disclose that treatment of melanoma cells with BSO for 72 hours decreased the total number of viable cells (57.4% of control), which was associated with >90% glutathione depletion (page 201, paragraph bridging left and right columns) and suggest that prolonged incubation of 48-96 hours causes increasing frequency of apoptosis/necrosis (page 203, left column). Bailey *et al.* teach "calibrated administration" of BSO by continuous infusion on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours (Abstract). Applicants are reminded that the Office does not have experimental facilities. As such, the burden is on Applicants to provide factual evidence that the co-administration of disulfiram and BSO for 3-4 days as taught in Cen *et al.* or BSO administered by the schedules taught in Bailey *et al.* would not have the effect of continuously maintaining decreased $[GSH]^2/[GSSG]$ ratio in the malignant cells and consequently continuously maintaining the dephosphorylated state of the RB in melanoma cells within a range of from 15 to 75 hours in order to span at least one cell cycle. This is especially true given the fact that Cen *et al.* explicitly teach that disulfiram induced apoptosis is associated with a decrease in the GSH:GSSG ratio, decrease in mitochondrial membrane potential, and a transient increase in cellular superoxide level (page 203, paragraph bridging left and right columns).

Response to Arguments

Applicant traverses the previous rejection of claims 26-29 and 34-35 (now claims 26 and 32) stating that Cen *et al.* concludes only that disulfiram-induced apoptosis is redox related but involves a different mechanism from BSO-induced apoptosis in tumor cells. Applicant further states that Cen *et al.* do not teach or suggest *in vivo* raising the E-dephosphorylate pRB with E-increasing agents and maintaining the raised E/dephosphorylated state of pRB with an enzyme deactivating agent to continuously maintain the dephosphorylated state of RB from between 15-75 hours. Applicant further cites the Hoffman Declaration, which alleges that the major cause of failure is the lack of awareness in the prior art of the nature of the intrinsic *in vivo* impediment to

effectiveness, and so the prior art does not (and cannot), it is alleged, teach or suggest a therapy of systematically treating cancer patients until the nature of the impediment is identified and overcome.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive.

Firstly, Applicant has presented no factual evidence that the co-administration of disulfiram and BSO for 3 or 4 days (*i.e.*, 72-96 hours) does not have the effect of raising the E-dephosphorylate pRB with E-increasing agent (*i.e.*, disulfiram) and maintaining the raised E/dephosphorylated state of pRB with an enzyme deactivating agent (*i.e.*, BSO) to continuously maintain the dephosphorylated state of RB from between 15-75 hours. The fact that Cen *et al.* did not measure E/dephosphorylated RB is not pertinent to the instant rejection. Cen *et al.* disclose that treatment of melanoma cells with BSO for **72 hours** decreased the total number of viable cells (57.4% of control), which was associated with >90% glutathione depletion (page 201, paragraph bridging left and right columns) and suggest that prolonged incubation of 48-96 hours causes increasing frequency of apoptosis/necrosis (page 203, left column). As such, the skilled artisan would clearly and unequivocally be motivated to administer BSO *in vivo* in a manner so as elicit the effect observed *in vitro*, such as by administering BSO in the treatment schedules suggested and motivated by Bailey *et al.* Likewise, Applicant's recognition of one mechanism through which disulfiram and BSO induce apoptosis of tumor cells is similarly not pertinent to the present rejection. The cited prior art suggests and motivates one skilled in the art to administer disulfiram and BSO together to treat melanoma, which, in the absence of evidence to the contrary, is a tumor comprising malignant cells having operative RB protein. The skilled artisan would reasonably expect that such a combination would be effective *in vivo*, given the proven efficacy of this combination *in vitro* and the knowledge in the art that BSO prolongs the survival of melanoma-bearing mice after *in vivo* administration. The Courts have continuously held that *in vitro* results are generally predictive of *in vivo* results, and Applicants have presented no factual evidence that such is not the case here. As such, the Examiner is not persuaded that an antitumor effect would not be expected to observed when a combination of disulfiram and BSO is administered to a subject.

Secondly, with regard to the Hoffman Declaration, the Examiner respectfully submits that the instant application and the Hoffman Declaration relate to a theoretical premise of continuously maintaining the dephosphorylated state of RB for between 15 and 75 hours, because, between administration periods, the RB can become phosphorylated, promoting cell proliferation (see Hoffman Declaration at paragraph 5). However, Cen *et al.* clearly teach that disulfiram and BSO, in combination, induce apoptosis. There is nothing in Cen *et al.* that suggests that cell proliferation occurred in the presence of these active agents. Disulfiram and BSO were administered for 3-4 days and there is nothing in Cen *et al.* to suggest that such administration does not or would not continuously maintain the dephosphorylated state of RB for 15 to 75 hours. Cen *et al.* explicitly teach that disulfiram induced apoptosis is associated with a decrease in the GSH:GSSG ratio, decrease in mitochondrial membrane potential, and a transient increase in cellular superoxide level (page 203, paragraph bridging left and right columns). Bailey *et al.* teach that BSO administered to human patients on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours produced "consistent, profound glutathione [GSH] depletion". Applicant has not presented a single example demonstrating that an effect not expected from the teachings of the prior art is observed when tumors are treated with disulfiram and BSO. Neither has Applicant provided a working example or factual evidence that any particular dosing regimen of the active agents is better than other dosing regimens.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 26, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and **Marikovsky** (USP No. 6,288,110; Issued Sep. 11, 2001) in view of **Bailey *et al.*** (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796).

Ali-Osman *et al.* disclose that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 30, and 32. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme. Figure 1 demonstrates that GCS is significantly

inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The reference further suggests 24-hour exposure to BSO to decrease glutathione content in glioma cells (Abstract; Fig. 5). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors, especially in view of the teachings therein where *in vitro* and ***in vivo*** studies and clinical trials in humans have shown GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy (page 1016, right column, "Discussion").

Marikovsky teaches administration of disulfiram to treat angiogenesis-dependent disorders such as neoplasms (Abstract). Examples of solid tumors that can be treated with disulfiram include bladder, breast, cervix, ear, esophogus, kidney, larynx, liver, lung, ovary, pancreas, prostate, skin, stomach, thyroid, urethra, and uterus carcinomas (col. 3, lines 1-5).

Marikovsky teaches administration of disulfiram of 1 mL of an aqueous solution comprising 0.1-0.5 mM disulfiram (25-120 mg) to mice bearing C6 glioma tumors (col. 6, lines 54-63; Table 1). Marikovsky further teaches that disulfiram induces apoptosis of endothelial cells (Figure 4).

Bailey *et al.* teach that increased intracellular glutathione has long been associated with tumor cell resistance to various cytotoxic agents (Abstract). BSO has been shown to enhance the cytotoxicity of chemotherapeutic agents *in vitro* and *in vivo* (*id.*). The authors studied the effects of BSO combined with melphalan in patients with advanced cancers. BSO was administered by continuous infusion on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours (Abstract). The treatment method produced "consistent, profound glutathione [GSH] depletion" (id.; Figure 1; Figure 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered BSO and BCNU in combination with disulfiram to a subject having cancer, especially gliomas. The skilled artisan would have been motivated to do

so because treatment with BSO has been shown in increase the cytotoxicity of glioma cells to BCNU and disulfiram is suggested in the prior art to be useful as a chemotherapeutic agent and has demonstrated *in vivo* efficacy also against glioma tumors. Furthermore, Bailey *et al.* teach that administration of BSO to human patients on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours produced "consistent, profound glutathione [GSH] depletion".

In the absence of evidence to the contrary, the glioma cells treated in Ali-Osman *et al.*, the cancers listed in Marikovsky *et al.* (including C6 glioma tumors), and the cancers treated in Bailey *et al.* have an "operative retinoblastoma protein" as recited in the instant claims. For example, Applicants teach that human RB protein is expressed in "every tissue type examined" (page 2, lines 28-29), plays a major role in a regulatory circuit in late G_1 (growth) phase (*id.* at lines 29-30), and is involved in regulating an elusive switch point between cell cycle, differentiation, and apoptosis (page 3, lines 3-4). As such, all cells in a subject would be expected to have an operative retinoblastoma protein. The effect recited in the instant claims (*i.e.*, dephosphorylizing the RB protein and maintaining a dephosphorylated state of the RB to induce apoptosis) would be a natural result of contacting glioma cells in a subject with BSO, BCNU, and disulfiram as suggested and motivated by the prior art. In fact, Bailey *et al.* teach that BSO administered to human patients on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours produced "consistent, profound glutathione [GSH] depletion". Applicant's recognition of the mechanism through which BSO and BCNU induce apoptosis of glioma cells is not a patentable distinction over the treatment method taught in the cited prior art.

Response to Arguments

Applicant traverses the previous rejection of claims 26-27 and 32-35 (now claims 26, 30, and 32), stating that Ali-Osman merely suggests that BCNU mitigates the cytotoxicity of BSO but does not teach or suggest *in vivo* raising the E-dephosphorylate pRB with E-increasing agents and maintaining the raised E/dephosphorylated state of pRB with an enzyme deactivating agent to continuously maintain the dephosphorylated state of RB from between 15-75 hours.

Applicant further cites the Hoffman Declaration, which alleges that the major cause of failure is the lack of awareness in the prior art of the nature of the intrinsic in vivo impediment to effectiveness, and so the prior art does not (and cannot), it is alleged, teach or suggest a therapy of systematically treating cancer patients until the nature of the impediment is identified and overcome.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive.

Firstly, Applicant has presented no factual evidence that the co-administration of disulfiram, BCNU, and BSO (as suggested and motivated by the teachings of the cited prior art) does not have the effect of raising the E-dephosphorylate pRB with E-increasing agent (*i.e.*, disulfiram) and maintaining the raised E/dephosphorylated state of pRB with an enzyme deactivating agent (*i.e.*, BSO and BCNU) to continuously maintain the dephosphorylated state of RB from between 15-75 hours as claimed. The fact that Ali-Osman *et al.* did not measure E/dephosphorylated RB is not pertinent to the instant rejection. Likewise, Applicant's recognition of one mechanism through which a combination of disulfiram, BCNU, and BSO might treat tumors as suggested and motivated by the cited prior art is similarly not pertinent to the present rejection. The cited prior art suggests and motivates one skilled in the art to administer disulfiram, BCNU, and BSO together to treat tumors, especially gliomas. The skilled artisan would reasonably expect that such a combination would be effective *in vivo*, given the proven efficacy of disulfiram *in vivo* and the teaching by Ali-Osman that *in vitro* and *in vivo* studies and clinical trials in humans have shown GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy. As such, the Examiner is not persuaded that an antitumor effect would not be expected to observed when a combination of disulfiram, BSO, and BCNU is administered to a subject.

Secondly, with regard to the Hoffman Declaration, the Examiner respectfully submits that the instant application and the Hoffman Declaration relate to a theoretical premise of continuously maintaining the dephosphorylated state of RB for between 15 and 75 hours, because, between administration periods, the RB can become phosphorylated, promoting cell proliferation (see Hoffman Declaration at paragraph 5). However, Ali-Osman *et al.* clearly teach that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of

BCNU and Marikovsky *et al.* unequivocally suggest and motivate treating tumors with disulfiram. Applicant has not presented a single working example or any factual evidence demonstrating that an effect not expected from the teachings of the prior art is observed when tumors are treated with disulfiram, BCNU, and BSO as suggested and motivated by the cited prior art. Neither has Applicant provided a working example or factual evidence that any particular dosing regimen of the active agents is better than other dosing regimens.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 26, 30, and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** (Issued July 8, 2003; Filed Sept. 8, 1999) in view of **Nagendra *et al.*** (Alcohol, 1994, vol. 11, pages 7-10), **Huang *et al.*** (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020), and **Hoffman *et al.*** (J. Theor. Biol., 2001, vol. 211, pages 403-407).

USP '987 discloses that disulfiram inhibits the growth of cancer cells (Abstract; col. 2, lines 38-44). Disulfiram can also be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18). '987 thus suggests administering disulfiram to treat tumors as recited in claims 26, 30, and 32.

Nagendra *et al.* disclose that chronic administration of disulfiram to rats affects GSH metabolism (Abstract). Administration of disulfiram led to a decrease in GSH with a concomitant increase in GSSG content, which would thus result in a decrease in the $[GSH]^2/[GSSG]$ ratio as instantly claimed. Brain glutathione reductase activity was also significantly depleted. The authors conclude that treatment with disulfiram decreases GSH content with a concomitant increase in GSSG level and perturbs the GSH/GSSG redox status, inducing oxidative stress on the brain. As Nagendra *et al.* is cited only for this general teaching, it follows that it is silent with respect to treating tumors.

Huang *et al.* disclose that the glutathione (GSH) level in hepatocytes increases during active proliferation (Abstract). The authors evaluated whether a similar increase is found in hepatocellular carcinoma (HCC). It is disclosed that GSH levels doubled in HCC as compared to normal liver (page 19). HepG2 liver cancer cells were grown with varying concentrations of

cysteine and it was found that cell growth increased with increasing cysteine concentration (page 19, right column). Further, BSO treatment decreased GSH levels and rates of growth. Cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls (page 19, right column). The authors disclose that GSH has been found to be elevated in a number of drug-resistant tumor cell lines including prostate, ovarian, lung and colorectal cancers (page 20, right column), thus suggesting that a decrease is GSH as achieved with BSO may result in a decrease in cell growth. Increased γ-L-glutamyl-L-cysteine synthetase (GCS) activity was found in the majority of these resistant tumor cells. The authors conclude that "an increase in the cellular GSH content may change the thiol-redox status of the cell that is proportional to $[GSH]^2/[GSSG]$" (page 21, right column). This change in redox state may then "affect the expression or activity of factors important for cell cycle progression". It is noted that BSO is recited as an agent that causes inhibition of the GCS enzyme (see instant claim 35). Huang *et al.* thus suggest and motivate the treatment of tumors having elevated GSH content as recited in instant claims 26 and 32.

Ali-Osman *et al.* disclose that depletion of GSH by BSO (currently being explored as a means of enhancing the efficacy of cancer chemotherapy and explicitly taught in Huang *et al.*) in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as for the treatment of cancer. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme (see instant claim 33). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors. The tertiary reference is silent with respect to disulfiram.

Hoffman *et al.* is cited for the general teaching that an elevated redox potential has been observed to be associated with the inability of retinoblastoma (RB) protein to be phosphorylated and with cell cycle arrest. As such, the authors suggest that an elevated redox potential can

inhibit phosphorylation of RB protein, which in turn will stop cell proliferation (page 403, paragraph bridging left and right columns), thus suggesting the treatment of cancers having an operative retinoblastoma (RB) protein *via* changes in redox potential. Hoffman *et al.* further teach that application of agents that decrease GSH will increase redox potential (page 405, right column, second paragraph under the heading "Model"). For example, Hoffman *et al.* teach that addition of BSO (which is taught by Huang *et al.* to decrease GSH) to fibroblasts and fibrosarcoma cells results in a threshold potential of between -196 and -218 mV that resulted in cessation of cell proliferation (page 406, left column, first paragraph under the heading "Application of the Model to Interpreting Published Data).

In view of the above disclosures, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is well known in the art that administration of BSO depletes GSH content and enhances the cytotoxicity of BCNU. Further, disulfiram has been shown to inhibit cancer cell proliferation and decrease GSH with a concomitant increase in GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in instant claim 26). It would have been obvious to combine disulfiram, BSO and/or carmustine (BCNU) to treat tumors because from the disclosures of the '987 patent, Huang *et al.*, Ali-Osman *et al.* and Nagendra *et al.* it is clear that disulfiram is effective at inhibiting cancer cell proliferation and that decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug BCNU. Thus, the skilled artisan would be imbued with at least a reasonable expectation that administering disulfiram would decrease GSH, increase GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in the instant claims), and be an effective treatment for tumors. In addition co-administration of BSO would be predicted to further decrease GSH content resulting in the sensitization of tumors to BCNU treatment.

Although ample motivation to combine the references is found in the teachings of the individual references as discussed *supra*, difulfiram and carmustine (*i.e.* BCNU) are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions

flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Further, the addition of BSO to a composition of disulfiram and BCNU would have been obvious given the teachings of Ali-Osman *et al.* who disclose that BSO enhances the anticancer activity of BCNU.

Response to Arguments

Applicant traverses the previous rejection of claims 26, 30, and 32, stating that this is a "piecemeal combination of prior art that ignores the unique type of in vivo synergistic effect of Applicant's specific combination of agents and specific regimen". In response, Applicants are respectfully requested to point to where any factual evidence of the alleged "synergistic effect" is found in the instant application. As far as the Examiner can see, Applicant proposes experiments to confirm the alleged activity of the claimed method, but no actual experiments were conducted by Applicants.

Secondly, Applicant argues that there are hundreds of agents that have been documented to have some anticancer effect and that the Examiner's position seems to be that it would be obvious to combine any agents that have already been mentioned in the literature as having some anticancer effect under some circumstances. The Examiner does not dispute this characterization. It is *prima facie* obvious to one skilled in the art to combine two known anticancer agents to treat cancer. Such combination chemotherapy is more than routine in the art of chemotherapy. Applicant has presented no factual evidence that the claimed combination of active agents provides and result that is not expected from the known efficacy of the individual agents.

Thirdly, Applicants argue that the "prior art is entirely unaware of the need to calibrate the Administration Frequency to the effective duration of the dephosphorylated state of RB/high

E". In response, the Examiner respectfully submits that the instant claims are not limited to any particular administration regimen. Rather, the claims simply recite "a calibrated administration frequency". The skilled artisan routinely optimizes doses and dosing regimens to achieve an antitumor effect *in vivo* whilst minimizing toxicity. Applicant has presented no factual evidence that he has discovered a particular administration regimen of the claimed active agents that achieves a result not expected from the teachings of the cited prior art. As has been discussed *ad nauseum* in the prosecution of the instant application, Applicant's recognition of a possible mechanism of action of the claimed compounds in treating cancer does not result in a patentable distinction over the prior art. The prior art clearly and unequivocally recognizes that BCNU, BSO, and disulfiram, alone and in combination with one another, are effective to induce apoptosis of cancer cells. The mechanism through which this occurs is not pertinent to the present rejection. Applicant has presented no factual evidence that there exists a particular administration frequency that achieves a result different from other administration frequencies.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 27-28 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** in view of **Nagendra *et al.***, **Huang *et al.***, **Ali-Osman *et al.***, and **Hoffman *et al.*** as applied to claims 26, 30, and 32 above, and further in view of **Ramachandran *et al.*** (Breast Cancer Research and Treatment, 1999, vol. 54, pages 269-278) and **Sharma *et al.*** (Clinical Cancer Research, July 2001, vol. 7, pages 1894-1900).

USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* teach as applied to claims 26, 30, and 32 above and are herein applied for the same teachings in their entirety. Claims 27-28 and 36-40 differ from USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* in that the cited references do not teach curcumin.

However, Ramachandran *et al.* teach that administration of curcumin to breast cancer cells induced apoptosis in breast cancer cells compared to a very low percentage of apoptosis in mammary epithelial cells (Abstract).

Sharma *et al.* teach that curcumin has been shown to prevent cancer of the skin, forestomach, duodenum, and colon of mice and in the tongue, colon, mammary glands, and

sebaceous glands of rates. Curcumin was also known to be associated with the regression of established malignancies in humans (page 1894, right column). Sharma et al. teach administration of capsules containing Curcuma extract which contained 36, 72, 108, 144, or 180 mg of curcumin to human patients having colon cancer daily for 29 days (Abstract; Table 1; page 1895, paragraph briding left and right columns). Five patients exhibited stable disease on CT scan (page 1897, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art to administer curcumin in combination with disulfiram, BCNU, and/or BSO to treat cancer in a subject. The skilled artisan would have been motivated to do so because curcumin has been taught to selectively induce apoptosis of breast cancer cells versus normal breast epithelial cells as well as to provide a clinical benefit in patients with colon cancer, and disulfiram, BCNU, and BSO have all been individually taught in the prior art to be effective antitumor agents alone and in combination with other chemotherapeutic agents. As such, it would have been obvious to one skilled in the art that curcumin combined with one or more of disulfiram, BCNU, and BSO would be effective to treat tumors in a subject.

Response to Arguments

As a first matter, Applicant incorrectly states that the Examiner rejected claims 30-31 over the cited prior art. In actuality, the Exmainer rejected claims 27 and 28. Applicant traverses the previous rejection of claims 27-28, stating that there exists no motivation to combine the individual active agents cited in the prior art and that the Examiner's position ignores the unique *in vivo* synergistic effect of Applicant's specific combination of agents and specific regimen. In response, Applicants are respectfully requested to point to where any factual evidence of the alleged "synergistic effect" is found in the instant application. As far as the Examiner aware, Applicant proposes experiments to confirm the alleged activity of the claimed method, but no actual experiments were conducted by Applicant.

The Examiner respectfully submits that the instant claims are not limited to any particular administration regimen. Rather, the claims simply recite "a calibrated administration frequency". The skilled artisan routinely optimizes doses and dosing regimens to achieve an antitumor effect in vivo whilst minimizing toxicity. Applicant has presented no factual evidence

that he has discovered a particular administration regimen of the claimed active agents that achieves a result not expected from the cited prior art. As has been discussed *ad nauseum* in the prosecution of the instant application, Applicant's recognition of one possible mechanism of action of the claimed compounds in treating cancer does not result in a patentable distinction over the prior art. The prior art clearly and unequivocally recognizes that BCNU, BSO, curcumin, and disulfiram, alone and in combination with one another, are effective to induce apoptosis of cancer cells and/or to treat cancer. The mechanism through which this occurs is not pertinent to the present rejection. Applicant has presented no factual evidence that there exists a particular administration frequency that achieves a result different from other administration frequencies.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 26-27, 30, 32, and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman (WO 02/056823; Published July 25, 2002) in view of **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and **Cen *et al.*** (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204).

Hoffman teaches a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). Treatment of tumors is taught at page 7, lines 25-32. The treatment of tumors having an operative RB protein as recited in claim 26 is taught at page 7, lines 22-24.

GSH depleting agents include oxidizers of GSH (*e.g.*, α-lipoic acid, hydrogen peroxide, ascorbic acid, quinones), agents that form adducts with GSH (*e.g.,* Michael acceptors), and inhibitors of GSH (*e.g.*, BSO) (pages 9-10).

Hoffman further teaches combinations comprising more than one GSH-depleting agent as recited in the instant claims (page 13, line 10 to page 14, line 6; page 16, line 5 to page 17, line 18; page 19, lines 11-33).

Hoffman teaches use of a composition of one or more GSH-decreasing agents wherein at least one of the agents is selected from foods, spices, and vitamins, preferably curcumin as recited in the instant claims (page 18, lines 27-31).

Hoffman teaches that conventional anticancer agents can be combined with GSH-depleting agents, including BCNU as recited in the instant claims (Table 1a).

Ali-Osman *et al.* disclose that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 30, and 32. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme. Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The reference further suggests 24-hour exposure to BSO to decrease glutathione content in glioma cells (Abstract; Fig. 5). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors, especially in view of the teachings therein where *in vitro* and ***in vivo*** studies and clinical trials in humans have shown GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy (page 1016, right column, "Discussion").

Cen *et al.* teach that redox regulation in melanoma cells is aberrant and that disulfiram induces apoptosis of metastatic melanoma cells at a dose of 25-50 ng/mL (Abstract; Fig. 1; Fig. 2). BSO, an inhibitor of γ-glutamyl-cysteine synthetase, as a single agent also increased apoptosis and slightly enhanced the level of apoptosis induced by disulfiram when co-administered for 3 or 4 days (Abstract; Table 1). The authors teach that BSO depletes intracellular glutathione and disulfiram reduces the ratio of reduced and oxidized glutathione (Abstract; Table 2). GSH depletion by BSO was known in the art to enhance the cytotoxic effects of 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, and melphalan, to inhibit DNA synthesis or growth of melanoma cell lines *in vitro*, and to prolong the survival of melanoma-bearing mice after *in vivo* administration (page 197, right column). BSO alone causes significant apoptosis in tumor cells, especially neuroblastoma (*id.*).

In view of the cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the claimed active agents to treat

tumors having an operative retinoblastoma protein. Hoffman explicitly suggests such combinations and further suggests that these combinations can be combined with other anticancer agents. Disulfiram was known in the art to decrease GSH and is thus an agent clearly encompassed by the teachings of Hoffman. BSO was known to increase the apoptosis induced by disulfiram, and BCNU was likewise known to be potentiated by BSO. As such, the skilled artisan would clearly expect that combinations of disulfiram, BCNU, and BSO, optionally further combined with curcumin as suggested and motivated by Hoffman, would be effective to treat tumors.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-27, 30, 32, and 36-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-15, 20, and 25-28 of copending Application No. 11/596,043. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods encompass administration of the same combinations of active agents to the same patient populations.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614